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Detection of magnesium compounds in dietary supplements and medicinal products by DSC, Infrared and Raman techniques

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Abstract The aim of this study was to learn to what extent the selected instrumental techniques, differential scanning calorimetry (DSC), as well as Fourier-transform infrared (FTIR) and Raman spectroscopies, can be used to detect both organic or inorganic magnesium compounds in the dietary supplements and medicinal products. Besides magnesium compounds as the active pharmaceutical ingredients (APIs), the preparations contain also other organic and inorganic APIs and several excipients. The study will be extended over the analysis of the products manufactured by various firms but containing the same API at different levels. In this way, it will be possible to assess the impact of excipients on the DSC scans and the FTIR and Raman spectra of a dominant constituent present in a studied preparation. The study on thirty commercially available dietary supplements and medicinal products has shown that in the majority of cases the DSC, FTIR and Raman techniques could be used for the detection of APIs in these commercial products. This was possible with the aid of the endothermic DSC peaks and the so-called matching factors of the FTIR and Raman spectra to those of substances used as standards. Both the complex composition and low levels of API in the studied preparations have been identified as the factors which have a strong impact on the usefulness of the three techniques for the detection of APIs in the dietary and medicinal products.

Keywords Magnesium compounds · DSC · FTIR · Raman · Quality control · Dietary supplements · Medicinal products

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Introduction

Quality evaluation of dietary supplements and medicinal products is mandatory from the point of view of efficacy, safety and stability of these preparations used for prophylactic and therapeutic purposes. Pharmaceutical law requires controlling compatibility of active pharmaceutical ingredients (APIs) and excipients with the appropriate standards [1, 2]. This obliges the producers to control the quality of all raw materials used in the manufacturing of medicinal products and to screen this process. Also the quality of a final drug product should be monitored. The investigation program comprises, among others, the surveillance of appearance of a pharmaceutical preparation, its labeling, quantitation of API in a dosage form, evaluation of physicochemical properties (hardness, density) and bioavailability of a drug form. Requirements for the quality control of dietary supplements are not so strict as in the case of medicinal products. However, in recent years there are legislation works conducted on the regulations, according to which the process of registration, manufacturing and quality control of dietary supplements should obey the same rules, as those referring to pharmaceuticals.

The necessity of permanent studies of APIs and medicinal products in a solid state is recommended, among others, by the regulations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), issued in the 1990-ties with the best of intentions to unify the requirements for new drugs implemented in the pharmaceutical market [3]. Recommendations of ICH, which are set in the both European and national pharmacopoeias [1, 2] oblige the manufacturers of medicinal products to conduct additional studies of all raw materials used in the formulation process. These studies have to encompass the

polymorphism, determination of crystal properties, particle size and specific surface, hygroscopic properties, solubility and chirality [4].

To perform these examinations, and to confirm the identity of all ingredients used by manufacturers, and also to quantify the dietary supplements and medicinal products, a sound knowledge of the technology of drug formulations and the methodology of drug analysis is necessary [5, 6]. The intensive progress in science and technology has resulted in introduction of highly advanced instrumental techniques to a modern pharmaceutical analysis. A screening of the literature data has shown that among others, thermoanalytical and spectroscopic techniques can be used to a large extent in the drug and food analysis. Numerous papers published recently revealed some examples of usefulness of differential scanning calorimetry (DSC) [7–11], thermogravimetry (TG) [7, 8, 12, 13], Fourier-transform infrared (FTIR) [10, 13–15], near infrared (NIR) [11, 14, 16] and Raman [9, 14, 17–20] techniques for analytical purposes.

For this reason, the aim of this study was to learn, to what extent selected thermoanalytical (DSC) and spectroscopic (FTIR, Raman) techniques could be useful for the evaluation of the composition of commercially available dietary supplements and medicinal products. The objective of the study involved detection of a particular substance in a studied preparation which contained several excipients along with the active substance. The DSC, FTIR and Raman techniques were selected because they enable to obtain quick result from a small sample without a time-consuming separation of API from a complex matrix. The features of these techniques are crucial from the point of view of quality control in the pharmaceutical industry. Recent tendencies lead to monitor the manufacturing process in the real time, enabling in this way that elimination of the control of a final product [18–21]. This new, original approach to the quality problem in the pharmaceutical industry is called Process Analytical Technology (PAT).

Experimental

Materials

A total number of thirty commercially available dietary supplements and medicinal products were analysed. These are as follows (manufacturers given in parentheses): Asmag, Asmag B, Asmag forte (Farmapol, Poznan, Poland); Aspargin, Filomag B_6 (Filofarm, Bydgoszcz, Poland); Asparaginum forte Mg + K (Polski Lek, Warsaw, Poland); Asparginian extra (Uniphar, Warsaw, Poland); Bio-Magnez (Pharma Nord, Vojens, Denmark); BluMag Jedyny (Hasco-Lek, Wroclaw, Poland); Cardiomin B_6 (Puritan's Pride, Bohema, USA); Chela-Mag B_6 (Olimp Labs, Debica, Poland); Dipromal 200 mg (ICN Polfa, Rzeszow, Poland); Dolomit VIS (VIS, Bytom, Poland); Laktomag B_6 (Chance, Czosnow, Poland); Maglek B_6 (Lek-Am, Zakroczyn, Poland); Magne B_6, Magne B_6 max (Sanofi-Aventis, Rzeszow, Poland); Magnefar B_6, Magnefar B_6 Cardio (Biofarm, Poznan, Poland); Magnesol 150 (Krka, Novo mesto, Slovenia); Magnezin (Polfa, Grodzisk Mazowiecki, Poland); Magvit B_6 (GSK Pharmaceuticals, Poznan, Poland); Mg B_6, NeoMag Cardio, NeoMag forte (Aflofarm, Ksawerow, Poland); Slow-Mag, Slow-Mag B_6 (Curtis Healthcare, Poznan, Poland); and Zdrovit magnez + vit. B_6, Zdrovit Magnum forte, Zdrovit Skurcz (NP Pharma, Ostrow Mazowiecki, Poland).

The active ingredients used were as follows: Mg acetate tetrahydrate, Mg carbonate, Mg chloride hexahydrate, Mg hydroxide, Mg oxide, pyridoxine hydrochloride (POCh, Gliwice, Poland); Mg citrate (Krka, Warsaw, Poland); Mg hydrogen aspartate tetrahydrate (Novichem, Chorzow, Poland); Mg lactate dihydrate (Sanofi-Biocom, Rzeszow, Poland); Mg valproate hydrate (ICN Polfa, Rzeszow, Poland); folic acid, tocopherol acetate (Sigma-Aldrich, Saint Louis, USA).

The excipients used were as follows: microcrystalline cellulose, sodium carboxymethyl cellulose (FMC Bio Polymer, Brussels, Belgium); corn starch (Sigma-Aldrich, Saint Louis, USA); ethylcellulose, potato starch, saccharose (MP Biomedicals LLC, Illkirch Cedex, France); lactose (PPH Galfarm, Krakow, Poland); methylcellulose, hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Tokyo, Japan); Mg stearate (Sinochem, Jiangsu, China); polyvinylpyrrolidone (Fluka, Siegen, Germany); sodium lauryl sulphate (Merck, Darmstadt, Germany); sodium starch glycolate (JRS Pharma, Rosenberg, Germany). All substances were used without further purification.

Methods

DSC scans were performed on a heat-flux DSC instrument (model 822^e, Mettler Toledo, Schwerzenbach, Switzerland) with a liquid nitrogen cooling system (Dewar vessel) and a STAR^e software. Samples under study, of approximately 4 mg in mass, were accurately weighed (±0.01 mg) and encapsulated in 40 μL flat-bottomed aluminium pans with crimped-on lids. Measurements were carried out over the range between 25 and 300 °C at a heating rate of 10 °C min^{-1} under nitrogen stream at a flux rate of 70 mL min^{-1}.

Indium (In) and zinc (Zn) standards were used to calibrate the DSC cell. Reference values for onset temperature and heat flow with the tolerance limits were as follows: 156.6 ± 0.3 °C and 28.45 ± 0.6 J g^{-1} for In; 419.6 ± 0.7 °C and 107.5 ± 3.2 J g^{-1} for Zn, whereas the

measured ones: 156.6 °C and 28.80 J g^{-1} (In); 420.1 °C and 110.7 J g^{-1} (Zn). Calibration and all the necessary adjustments were performed with aid of the computer program Calib DSC Total In/Zn (Mettler Toledo, Schwerzenbach, Switzerland).

FTIR spectra were recorded on a Nicolet 380 FTIR spectrometer (Thermo Fischer Scientific, Madison, USA) with a DTGS KBr detector and an OMNIC software. The analysed samples were prepared as KBr pellets with the aid of a hydraulic press (Specac, Orpington, UK). Each pellet was prepared from a 1-mg sample and 100 mg of a spectroscopy-grade KBr (Merck, Darmstadt, Germany). Measurements were carried out over the spectral range of 4,000–400 cm^{-1} with spectral resolution of 4 cm^{-1} Before each measurement, background spectra were taken with average16 scans.

Raman spectra were recorded on a DXR SmartRaman spectrometer (Thermo Fisher Scientific, Madison, USA). The spectrometer was equipped with a 15-mW DXR 780 nm laser with a slit width of 25 μm, Raleigh filter, CCD detector and an OMNIC software. The measurements were run over the range of 3,413–99 cm^{-1}. Exposure time was 1 s (twice). DSC, FTIR and Raman experiments were repeated at least in triplicate.

Results and discussion

To check the utility of DSC, FTIR and Raman techniques as a potential approach enabling detection of a drug substance in dietary supplements and medicinal products, thirty preparations commonly available in Poland were chosen. Mg salts of organic acids (acetate, citrate, diglycinate, hydrogen aspartate, lactate, valproate) and inorganic Mg compounds (carbonate, chloride, hydroxide, oxide) were present in the studied preparations as dominant active ingredients. Furthermore, some preparations also containing varying amounts of other organic and inorganic salts of potassium (aspartate, citrate, gluconate, hydrogen aspartate, bicarbonate, chloride) and of calcium (citrate, hydrogen aspartate, carbonate). Organic APIs, such as pyridoxine hydrochloride (vitamin B_6), aspartic and folic acids and tocopherol acetate were also present in some samples. Merely eleven preparations (Asmag, Asmag forte, Asparagin, Asparaginum forte Mg + K, Asparginian extra, Bio-Magnez, Dipromal 200 mg, Dolomit VIS, Magnesol 150, Magnezin, Slow-Mag) did not contain vitamin B_6.

Fourteen out of thirty preparations were medicinal products containing Mg salts of organic acids as APIs. These were: Asmag, Asmag B, Asmag forte, Aspargin, Dipromal 200 mg, Filomag B_6, Laktomag B_6, Maglek B_6, Magvit B_6 and Magne B_6, whereas Dolomit VIS, Magnezin, Slow-Mag and Slow-Mag B_6 including inorganic Mg compounds. Medicinal products under study constitute the so-called over-the-counter (OTC) drugs.

The majority of dietary and medicinal products were in the form of tablets. The remaining ones were in coated tablets (Cardiomin B_6, Dipromal 200 mg, Magne B_6 max, Mg B_6, NeoMag Cardio, NeoMag forte, Zdrovit Skurcz), gastro-resistant tablets (Magne B_6, Magvit B_6, Slow-Mag, Slow-Mag B_6) and effervescent tablets (Magnesol 150, Zdrovit magnez + vit. B_6, Zdrovit Magnum forte). Moreover, two dietary supplements were in the form of capsules (Chela-Mag B_6, BluMag Jedyny). Hence, all the preparations studied included various numbers and quantities of excipients, ensuring optimal activity of the dosage forms from the point of view of pharmacotherapy. Chemical analysis includes usually separation of APIs from excipient this being a time- and work-consuming process. Hopefully, application of DSC, FTIR, and Raman techniques could allow for elimination of this step of analytical procedure.

Differential scanning calorimetry

DSC is a thermoanalytical technique where energy changes in a sample are monitored with temperature [6]. The heat flow to or from the sample and to or from the reference is monitored as a function of temperature or time. Such measurements provide qualitative and quantitative information about physical and chemical changes involving endothermic and exothermic processes, or changes in heat capacity, i.e., thermal transformations. These features of the DSC were used for the study of thirty dietary supplements and medicinal products and dominant constituents present in these preparations. The DSC scans of the drug substances are shown in Fig. 1, while the data characterising their thermal behaviour over the temperature range of 25–300 °C

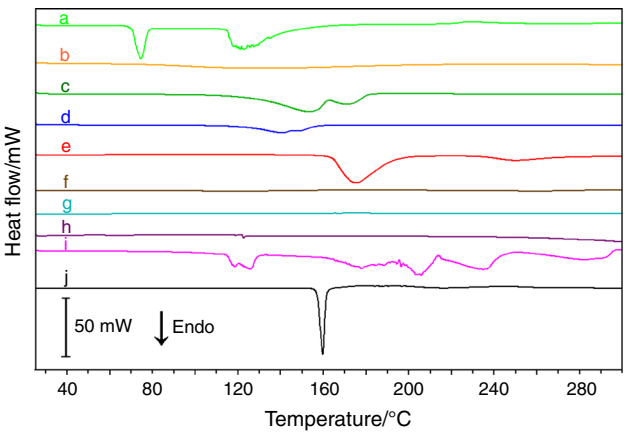

Fig. 1 DSC scans of magnesium (*a*) acetate tetrahydrate, (*b*) citrate, (*c*) lactate dihydrate, (*d*) valproate, (*e*) hydrogen aspartate tetrahydrate, (*f*) oxide, (*g*) hydroxide, (*h*) carbonate, (*i*) chloride hexahydrate and (*j*) pyridoxine hydrochloride

Table 1 Active ingredients included in the studied dietary supplements and medicinal products

No.	Active ingredients	Thermal process [22, 23]	Endothermic DSC peak/°C	Heat of transition/J g^{-1}
1	Magnesium acetate tetrahydrate	80 °C dehydration	73.24	178.39
		323 °C decomposition	121.67	376.36
2	Magnesium citrate	–	130.78	467.90
3	Magnesium lactate dihydrate	–	152.26	270.48
			171.68	91.64
4	Magnesium valproate hydrate	–	139.33	35.66
			148.89	11.95
5	Magnesium hydrogen aspartate tetrahydrate	–	173.83	579.34
6	Magnesium oxide	2,800 °C melting	–	–
7	Magnesium hydroxide	350 °C dehydroxylation	–	–
8	Magnesium carbonate	350 °C decarboxylation	–	–
9	Magnesium chloride hexahydrate	116–118 °C dehydration	117.49	154.38
			196.66	182.06
10	Pyridoxine hydrochloride	160 °C melting with decomposition	157.11	211.81

are listed in Table 1. These data revealed that with the exception of Mg chloride hexahydrate, all the remaining inorganic Mg compounds (oxide, hydroxide, carbonate) did not undergo any thermal transformation over the range studied [22]. Because MgO melts at 2,800 °C, $Mg(OH)_2$ dehydroxylates and $MgCO_3$ decarboxylates above 350 °C, there are no DSC peaks between 25 and 300 °C that can be used for the detection of dominant compounds in the dietary and medicinal products. In this case the DSC scans can be used for detection the organic active substances, e.g., vitamin B_6, organic salts of magnesium, potassium and calcium or excipients, e.g., saccharose, lactose, microcrystalline cellulose. Merely $MgCl_2{\cdot}6H_2O$ is characterised by several endothermic DSC peaks owing to its step-by-step dehydration.

Thermal decomposition of Mg salts of organic acids has been studied previously [23]. The results have shown that the evolution of crystallization water takes place in the range between 35 and 255 °C for Mg acetate, Mg lactate, Mg valproate and Mg hydrogen aspartate. TG curves revealed that Mg valproate and Mg hydrogen aspartate dehydrate in one stage while dehydration of Mg acetate and Mg lactate comprised three and two stages, respectively. These findings were confirmed by endothermic DSC peaks in Fig. 1, scans a, c–e. An exception to this scheme is Mg citrate which is characterised by a shallow endothermic peak over the range of 73 and 181 °C peaked at 131 °C (scan b). Hence, in the case of Mg salts of organic acids and pyridoxine hydrochloride, strong and sometimes narrow endothermic DSC peaks would constitute a basic criterion for the detection of these substances.

Results acquired from the DSC scans of thirty dietary and medicinal products are compiled in Table 2. Their preliminary inspection has shown a strong impact of the quantity of active ingredients based on the mass unit of a tablet on the ability to identify an API in a preparation. The data in Table 2 calculated on the basis of the dose of an active substance and the mean tablet mass designed for 10 units of tablets have shown that the preparations can be differentiated by the percentage contents of an API. Generally, the dietary supplements and medicinal products contained higher amounts of Mg salts of organic acids ($\sim$50–90 % of the tablet mass) than inorganic compounds, with the exception of the dietary supplement BluMag Jedyny. It contains more than 93 % of MgO per tablet mass.

For the majority of preparations under study, manufacturers provide information on the content of Mg compounds recalculated as Mg^{2+} ions, regardless of the fact that some of them contain two or three Mg compounds. For instance, for Bio-Magnez the content of Mg acetate, $MgCO_3$ and $Mg(OH)_2$ is given as 19.9 % of Mg^{2+} ions while Cardiomin B6 comprising Mg hydrogen aspartate, Mg citrate and MgO is labeled as containing 12.4 % of Mg^{2+} ions. For this reason, it is impossible the precisely define the percentage of each constituent in a particular preparation.

Interpretation of the DSC scans of all dietary supplements and medicinal products revealed that endothermic peaks due to the dehydration of Mg salts can be used for the detection of APIs in the studied samples. This can be exemplified by a DSC scan of the drug Dipromal 200 mg (Fig. 2) which shows the presence of Mg valproate in the sample as compared to the scan of Mg valproate used as a standard. Similarly, in the DSC scan of the dietary supplement Bio-Magnez there is an endothermic peak

Table 2 Results of DSC, FTIR and Raman analyses of the dietary supplements and medicinal products with magnesium compounds

No.	Dietary supplements and medicinal products	Dominant active ingredients	Dose of API/g	Average tablet mass/g	Content of API in tablets/%	DSC peak/ °C	Heat of transition/J g^{-1}	Matching factor FTIR/%	Matching factor Raman/%
Preparations containing Mg salts of organic acids									
1	Bio-Magnez	Mg acetate	0.200[a]	1.0065	19.9[a]	76.46	74.56	39.68	44.30
		Mg carbonate						49.50	57.60
		Mg hydroxide						61.70	27.95
2	Dipromal 200 mg	Mg valproate	0.200	0.3283	60.9	136.12	100.00	96.60	10.85
3	Mg B_6	Mg lactate	0.050[a]	0.6467	7.7[a]	161.99	365.01	44.82	61.73
4	Maglek B_6	Mg lactate	0.500	0.8014	62.4	162.25	502.65	44.04	62.03
5	Magvit B_6	Mg lactate	0.500	0.7320	68.3	160.43	298.97	44.82	61.63
6	Magne B_6	Mg lactate	0.500	0.9049	55.3	166.56	294.93	44.34	56.61
7	Magnesol 150	Mg citrate	0.150[a]	6.4900	2.3[a]	–	–	21.94	15.20
8	Magne B_6 max	Mg citrate	0.100[a]	0.7859	12.7[a]	185.37	436.74	44.68	17.63
9	Magnefar B_6	Mg citrate	0.500	0.8491	58.9	181.85	447.01	43.98	17.88
10	Magnefar B_6 Cardio	Mg citrate	0.033[a]	0.8827	3.7[a]	174.79	270.20	49.07	20.99
11	Asmag	Mg hydrogen aspartate	0.300	0.3942	76.1	175.36	406.73	97.78	87.71
12	Asmag Forte	Mg hydrogen aspartate	0.500	0.5672	88.2	173.74	529.73	98.92	93.84
13	Asmag B	Mg hydrogen aspartate	0.300	0.3990	75.2	179.86	491.53	97.88	93.60
14	Filomag B_6	Mg hydrogen aspartate	0.600	0.6985	85.9	172.95	592.01	99.03	93.18
15	Laktomag B_6	Mg hydrogen aspartate	1.00	1.3388	74.7	173.37	260.85	99.04	94.19
16	Aspargin	Mg hydrogen aspartate	0.25	0.6928	36.1	167.93	370.76	77.78	86.38
17	Asparaginum forte Mg + K	Mg hydrogen aspartate	0.015[a]	0.2830	5.3[a]	–	–	14.37	11.41
		Mg carbonate						54.86	5.75
18	Cardiomin B_6	Mg hydrogen aspartate	0.250[a]	2.0163	12.4[a]	181.11	18.53	14.57	10.78
		Mg citrate						0.91	2.54
		Mg oxide						16.00	9.03
19	Chela-Mag B_6	Mg diglycinate	0.555	0.6067	91.5	146.17	151.31	43.28	27.44
Preparations containing inorganic Mg compounds									
20	BluMag Jedyny	Mg oxide	0.622	0.6666	93.2	–	–	0.01	7.74
21	Zdrovit Skurcz	Mg oxide	0.050[a]	0.5440	9.2[a]	–	–	6.27	6.47
22	Magnezin	Mg carbonate	0.500	0.6713	74.5	–	–	50.91	78.07
23	NeoMag forte	Mg carbonate	0.100[a]	0.5558	18.0[a]	–	–	51.96	81.78
24	Zdrovit magnez + vit B_6	Mg carbonate	0.100[a]	4.1020	2.4[a]	–	–	0.01	2.76
25	Zdrovit Magnum Forte	Mg carbonate	0.300[a]	4.4640	6.7[a]	–	–	7.80	24.85
26	Dolomit VIS	Mg carbonate	0.032[a]	0.4922	6.5[a]	–	–	5.16	15.59

Table 2 continued

No.	Dietary supplements and medicinal products	Dominant active ingredients	Dose of API/g	Average tablet mass/g	Content of API in tablets/%	DSC peak/ °C	Heat of transition/J g^{-1}	Matching factor FTIR/%	Matching factor Raman/%
27	Asparaginian extra	Mg carbonate	0.036[a]	0.8111	4.4[a]	–	–	47.21	5.01
28	NeoMag Cardio	Mg carbonate	0.035[a]	0.6197	5.6[a]	–	–	34.86	18.34
29	Slow-Mag	Mg chloride	0.535	0.9366	57.1	118.15	218.96	88.03	2.70
30	Slow-Mag B_6	Mg chloride	0.535	0.9334	57.3	117.04	78.91	84.57	3.88

[a] Content of active ingredients in preparations calculated as Mg^{2+} ions

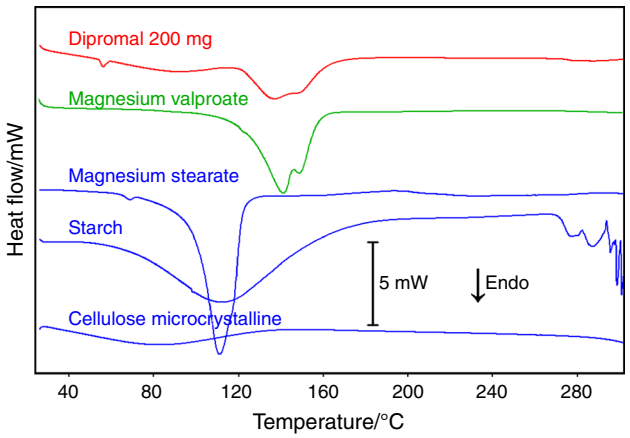

Fig. 2 DSC scans of medicinal product Dipromal 200 mg; magnesium valproate as API; and excipients

assigned to the dehydration of Mg acetate (Table 2). Other active ingredients, $MgCO_3$ and $Mg(OH)_2$, did not undergo any thermal processes over the temperature range studied.

Four dietary and medicinal products: MgB_6, Maglek B_6, Magvit B_6 and Magne B_6 contain almost identical quantities of APIs (Mg lactate and pyridoxine hydrochloride) but they are produced by different manufacturers, and due to this they differ by the kind and quantities of excipients. Their DSC scans display strong, broad peaks between 125 and 175 °C which confirm the presence of Mg lactate. There is no clear-cut signal originating from vitamin B_6 because it is present as a minor constituent (5–6 mg). DSC scans of other dietary supplements: Magne B_6 max, Magnefar B_6 and Magnefar B_6 Cardio clearly reflect dehydration of Mg lactate that enables its identification. However, there is no endothermic peak assignable to Mg lactate in a scan of Magnesol 150 tablets. Probably, thermal effects caused by a violent reaction between effervescent agents, sodium bicarbonate and citric acid, with releasing of carbon dioxide, preclude identification of characteristic DSC peaks of its dehydration.

Similar to Mg citrate and Mg lactate, high levels of Mg hydrogen aspartate in the tablets of Asmag, Asmag Forte, Asmag B, Filomag B_6, Laktomag B_6 and Aspargin (medicinal products) enable easy detection of this salt by a large endothermic DSC peak due to the dehydration of API (Table 2). The dietary supplements: Asparaginum forte Mg + K and Cardiomin B_6 also contain Mg hydrogen aspartate, but their composition is more complex. In the former case, there are calcium carbonate and potassium hydrogen aspartate and chloride, while the latter sample contains also Mg citrate and MgO, potassium hydrogen aspartate, gluconate and citrate, and calcium hydrogen aspartate, citrate and oxide. For this reason, the DSC scans show small peaks of a low intensity which are difficult for interpretation. There are no clear-cut signals originating

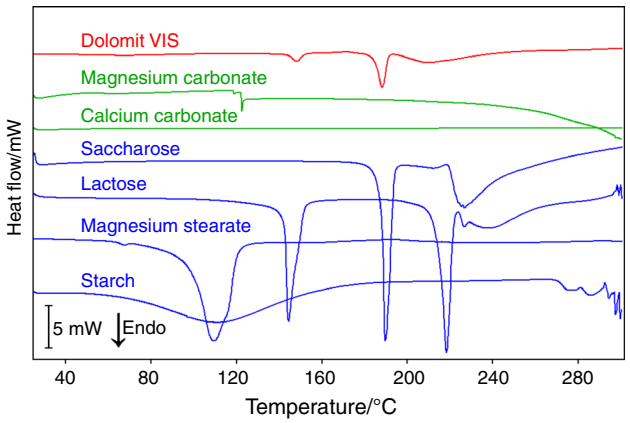

Fig. 3 DSC scans of medicinal product Dolomit VIS; magnesium carbonate and calcium carbonate as APIs; and excipients

from Mg compounds present in the preparations as dominating ingredients.

Another group of dietary and medicinal products contains inorganic Mg compounds as APIs. Active substances comprised in the dietary supplements BluMag Jedyny and Zdrovit Skurcz (MgO) and in the tablets of Magnezin, NeoMag forte, Zdrovit magnez + vit B_6, Zdrovit Magnum Forte, Dolomit VIS, Asparaginian extra, NeoMag Cardio, Slow-Mag and Slow-Mag B_6 ($MgCO_3$) could not be identified by DSC because endothermic peaks assignable to MgO and $MgCO_3$ were missing. As shown in Fig. 3 (Dolomit VIS), small endothermic DSC peaks are due to the melting of excipients, lactose (~143 °C) and saccharose (~189 °C). On the other hand, the DSC scans of Slow-Mag and Slow-Mag B_6 indicated that $MgCl_2 \cdot 6H_2O$ could be easily identified in the medicinal products based on characteristic endothermic DSC peaks due to dehydration.

Infrared and Raman spectroscopy

Infrared (IR) and Raman spectroscopies are vibrational techniques [6]. They are non-destructive and extremely useful for providing structural information about molecules in terms of their functional groups, the orientation of those groups and information on isomers. In association with chemometric methods they can also be used to provide quantitative information [14–16]. IR and Raman spectroscopies are similar insofar as they both produce spectra based on vibrational transitions within a molecule and use the same spectral regions [6]. They differ in the way that the observation and measurement are achieved, since IR is an absorption (transmission) method, while Raman is a scattering method. The use of an interferometer to obtain the IR spectra caused that a FTIR spectrometer has become a commonly used instrument in scientific and industrial pharmaceutical labs. The advantages of FTIR are greater sensitivity (signal-to-noise ratio) owing to the use of certain detectors and a greater speed owing to simultaneous acquisition of data (simultaneous measurement at all wavelengths).

The FTIR spectra of the drug substances taken over the range of 4,000–400 cm^{-1} (Fig. 4) consist of a complex series of sharp peaks corresponding to the vibrations of spectral groups within the molecule. Two spectral ranges, 3,600–2,800 cm^{-1} and 1,800–1,000 cm^{-1}, were chosen for interpretation [15]. The fingerprint region (1,800–1,000 cm^{-1}) is most valuable because it is partially devoid of absorption bands arising from excipients, and thus enables a better recognition of changes in the structure of the Mg salts. The region is complemented by bands extending from 3,600 to 2,800 cm^{-1}, frequently highlighting the presence of the N–H, C–H and O–H bounds in the molecule. In this area, characteristic bands of the O–H and C–H stretching vibrations are observed when carbohydrates (glucose, lactose, saccharose, starch, cellulose) are used as excipients. The literature data on the characteristic IR absorption frequencies of common functional groups were used for assigning bands observed in a spectrum of a Mg compound to chemical groups in this drug substance [14, 24, 25].

FTIR analysis was conducted of dietary and medicinal products containing Mg compounds and several excipients. By comparing these spectra with those in Fig. 4, it can be stated that despite complex chemical composition of the studied samples their spectra were the consequences of vibrational transitions within the molecule of a dominant constituent that is a Mg salt of organic acid. For example,

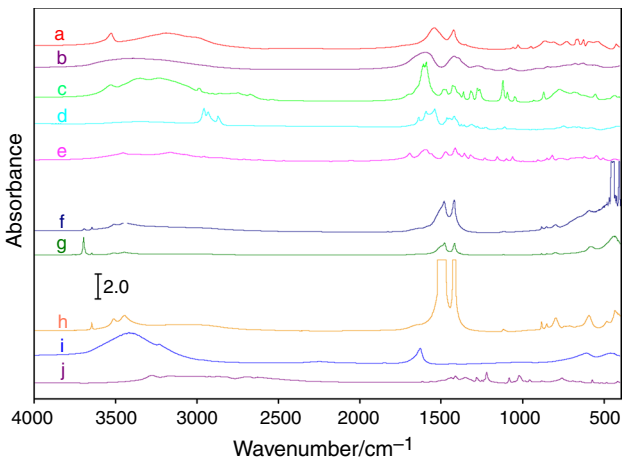

Fig. 4 FTIR spectra of magnesium (*a*) acetate tetrahydrate, (*b*) citrate, (*c*) lactate dihydrate, (*d*) valproate, (*e*) hydrogen aspartate tetrahydrate, (*f*) oxide, (*g*) hydroxide, (*h*) carbonate, (*i*) chloride hexahydrate and (*j*) pyridoxine hydrochloride

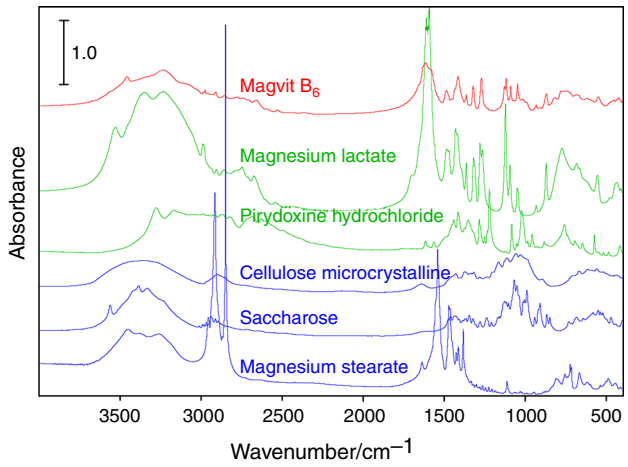

Fig. 5 FTIR spectra of medicinal product Magvit B_6 containing magnesium lactate and pyridoxine hydrochloride as APIs and excipients

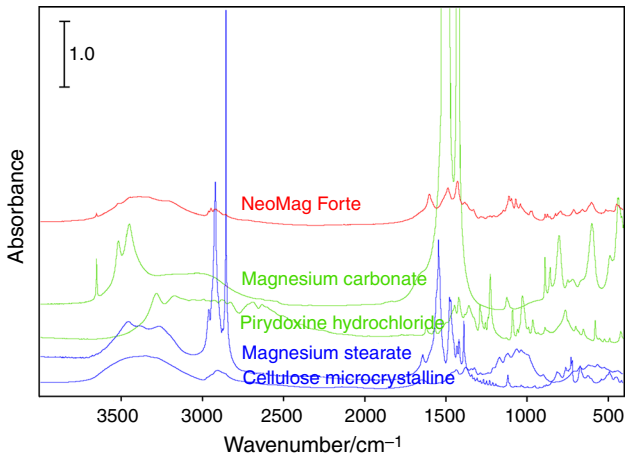

Fig. 6 FTIR spectra of dietary supplement NeoMag Forte containing magnesium carbonate and pyridoxine hydrochloride as APIs and excipients

the spectrum of Magvit B_6 shows a close similarity to that of Mg lactate (Fig. 5). The small difference in the shape of both spectra probably results from the excipients present. On the other hand, there is no similarity between the FTIR spectra of inorganic Mg compounds and those of the dietary supplements and medicinal products containing these substances. This is presumably due to the lack of characteristic and strong peaks corresponding to the vibrations of spectral groups within the MgO molecule (Fig. 4, spectra f and g). An exception provides some tablets containing $MgCO_3$ and $MgCl_2{\cdot}6H_2O$. As shown in Fig. 6, the spectrum of the NeoMag Forte tablets reflects the presence of $MgCO_3$ in this dietary supplement. The same conclusions can be drawn for the gastro-resistant tablets, Slow-Mag and Slow-Mag B_6. In the latter case, apart from $MgCl_2{\cdot}6H_2O$, vitamin B_6 is also present in the tablets.

Taking all above into consideration, the so-called matching factor was designed, which determines in percents the extent of matching of the spectrum of a studied preparation to that of the Mg salt. This was the basis for confirmation of the presence of active ingredients in the analysed preparations. The computer-generated matching factors for all the dietary and medicinal products are listed in Table 2. The data show that for Mg hydrogen aspartate, which is a dominant constituent in six medicinal products, the matching coefficients of FTIR spectra of the drug products with this salt to the spectrum of Mg hydrogen aspartate fall within the range of 97.78–99.04 %. An exception provides the matching factor for the Aspargin which is lower (about 78 %). This indicates that the spectra of these preparations nearly overlap that of Mg hydrogen aspartate. The close similarity to the spectrum of Mg valproate also show the tablets of Dipromal 200 mg (96.60 %), whereas the matching factors of the spectra for preparations comprising Mg lactate and Mg citrate to the FTIR spectra of these constituents fall in the range of 44.04–44.82 % and of 43.98–49.07 %, respectively. In the latter case, the matching factor for the effervescent tablets of Magnesol 150 was about 22 %, thus being of no practical importance from the point of detection of the constituent in this dietary supplement.

With the exception of some preparations with $MgCO_3$, such as the Bio-Magnez, Asparaginum forte Mg + K, Magnezim, NeoMag Forte, Asparaginian extra and NeoMag Cardio, the matching factors for FTIR spectra of the other tablets with $MgCO_3$ or MgO in relation to these constituents as the reference are generally low, varying between 0.01 and 16.00 %. This suggests that similar to the effervescent tablets of Magnesol 150, effervescent agents present in the tablets of Zdrovit magnez + vit. B_6 and Zdrovit Magnum forte, and some of the excipients in the tablets of Dolomit VIS cause that their spectra differ significantly from those of $MgCO_3$ used for comparison, precluding its identification.

Raman spectroscopy is complementary to the IR and is primarily a non-contact quantitative technique [6]. Polar functional groups with low symmetry generally give strong IR signals while molecules with polarisable functional groups with high symmetry generally give strong Raman signals. Hence, strong IR absorptions appear usually as weak Raman ones and vice versa. Moreover, the Raman technique is not as sensitive to the environment of the molecule as is IR. For this reason, Raman spectra for thirty dietary and medicinal products were acquired over the spectral range of 3,413–99 cm^{-1} together with those of Mg compounds present in these products. The spectra in Fig. 7 show that organic fragments of Mg compounds (spectra a–e) and vitamin B_6 (spectrum j) generate Raman frequencies for their characteristic functional groups which can be used for

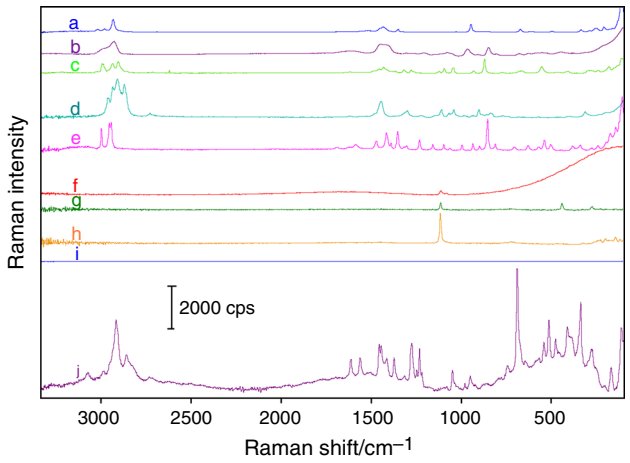

Fig. 7 Raman spectra of magnesium (*a*) acetate tetrahydrate, (*b*) citrate, (*c*) lactate dihydrate, (*d*) valproate, (*e*) hydrogen aspartate tetrahydrate, (*f*) oxide, (*g*) hydroxide, (*h*) carbonate, (*i*) chloride hexahydrate and (*j*) pyridoxine hydrochloride

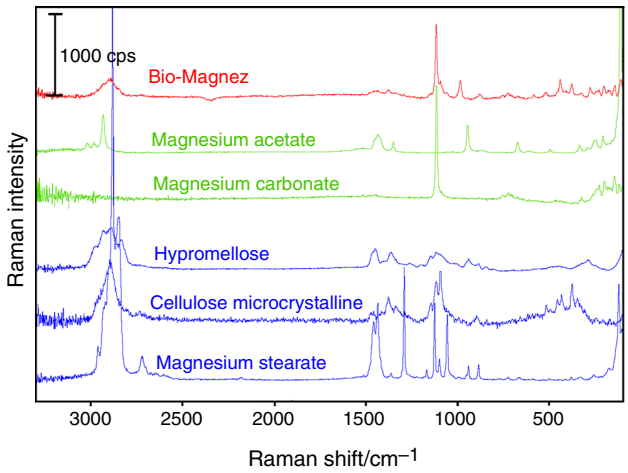

Fig. 8 Raman spectra of dietary supplement Bio-Magnez containing magnesium acetate, magnesium carbonate and magnesium hydroxide as APIs and excipients

the detection of the dominant ingredients in the studied samples [14, 25]. On the other hand, Raman spectra of inorganic Mg compounds are not characteristic because particular Raman signals associated with different vibrational or rotational motions of the molecules in the sample have either low intensity (spectra f, g) or are missing at all (spectrum i). This is inconvenient from the point of view of identification of Mg compounds. Merely Mg carbonate (spectrum h) has an intensive Raman signal which can be used for the detection of this salt.

Data in Table 2 show that with Mg hydrogen aspartate and Mg lactate, which are the dominant constituents in the preparations, the matching coefficients of particular Raman spectra of the medicinal products to the spectra of these salts fall within the range of 86.38–94.19 % and 56.61–62.03 %, respectively. This indicates that the spectra of the preparations nearly overlap those of Mg hydrogen aspartate and Mg lactate. The closest similarity to the spectrum of Mg hydrogen aspartate shows the tablets of Laktomag B_6, but despite the relatively low quantity of this salt in the tablets of Aspargin (36.1 %), the matching factor of the spectrum for this preparation to the Raman spectrum of Mg hydrogen aspartate exceeds 77 %. Also, owing to the complex composition of the Asparaginum forte Mg + K and Cardiomin B_6 tablets, similarly as in the case of DSC and FTIR results, the presence of Mg hydrogen aspartate and others drug substances in these dietary supplements is reflected by low matching factors. Furthermore, the matching factors for the dietary supplements containing Mg citrate fall in the range of 15.20–20.99 % which are of no practical importance for the detection of this constituent. As shown in Table 2, a similar conclusion can be drawn for the Dipromal 200 mg tablets.

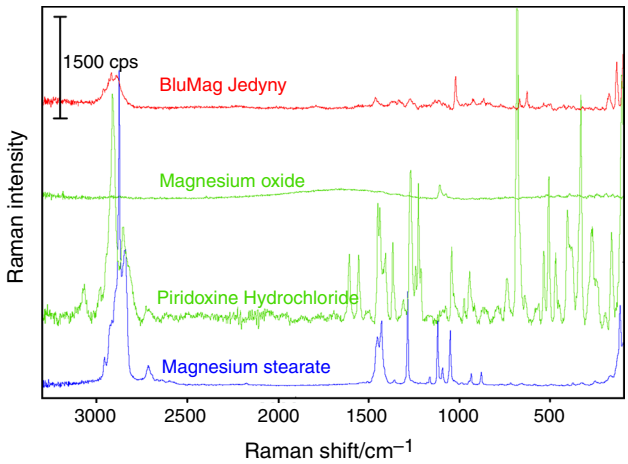

Fig. 9 Raman spectra of dietary supplement BluMag Jedyny containing magnesium oxide and pyridoxine hydrochloride as APIs and excipients

The matching factors of the Raman spectrum of the Bio-Magnez tablets in relation to those of Mg acetate, $MgCO_3$ and $Mg(OH)_2$ give the values partially comparable to those obtained by the FTIR technique (Table 2). As shown in Fig. 8 (Bio-Magnez), the presence of Mg acetate and $MgCO_3$ could be detected in the dietary supplement based on its Raman spectrum. With the exception of the Magnezin and NeoMag forte tablets, for which the matching factors were, respectively, 78.07 and 81.78 %, the presence of MgO (Fig. 9), $MgCO_3$ and $MgCl_2{\cdot}6H_2O$ in the other preparations could not be confirmed by the matching factors of the Raman spectra of these preparations in spite of a high content of the dominant constituents.

Conclusions

This study has shown that in the majority of cases, the DSC, FTIR and Raman techniques could be used for the detection of the dominant constituent in the dietary supplements and medicinal products. A strong impact on the detection ability of these techniques has the content of Mg compounds used as APIs. To identify the dominant constituents the well-shaped endothermic DSC peaks due to the dehydration of Mg compounds and the matching factors of the FTIR and Raman spectra to those of Mg compounds (reference substances), were used. The results obtained by the FTIR and Raman spectroscopies were complementary to those obtained by DSC. Furthermore, the way of performing the measurements by these techniques is simple and does not require preliminary preparation of a sample for analysis.

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